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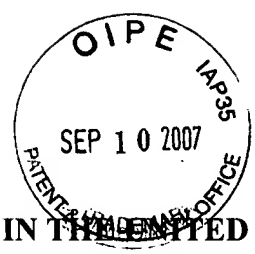

PATENT APPLICATION
Attorney's Docket No.: 1855.1004-002 (LKS94-04A2)

AF/1644

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Michael J. Briskin		
Application No.:	08/875,849	Group:	1644
Filed:	September 8, 1997	Examiner:	R. Schwadron, Ph.D.
Confirmation No:	4411		
For:	MUCOSAL VASCULAR ADDRESSINS AND USES THEREOF		

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REPLY BRIEF

MS Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Reply Brief is being filed in response to the Examiner's Answer mailed from the U.S. Patent and Trademark Office on July 6, 2007 in the above-identified application.

I. STATUS OF CLAIMS

Claims 24-26, 28-32, 101, 105-108, 111-113, 115-121 and 124-160 are pending.

Claims 1-23, 27, 33-100, 102-104, 109, 110, 114, 122 and 123 were canceled. Claims 101, 117 and 151 are withdrawn from consideration as being drawn to non-elected species. Claims 24-26, 28-32, 105-108, 111-113, 115, 116, 118-121, 124-150, and 152-160 are rejected.

Claims 24-26, 28-32, 105-108, 111-113, 115, 116, 118-121, 124-150, and 152-160 are on appeal. A copy of the appealed claims appears in the Claims Appendix of the Amended Appeal Brief, filed on August 16, 2006.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 24-26, 28-32, 105-108, 111-113, 115, 116, 118-121, 124, 125, 136-150 and 152-160 are properly rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that is not supported by adequate written description.

B. Whether claims 24-26, 28-31, 105-108, 111, 113, 115, 116, 118, 120, 121, 124, 126-142, 144-147, 149, 150, 152, 154, 155 and 157-160 are properly rejected under 35 U.S.C. § 103(a) as being obvious over Butcher *et al.* (WO 94/13312; Reference AD of record) in view of Vonderheide *et al.* (U.S. Patent No. 5,599,676; Reference AB of record) and Erle *et al.* (*J. Immunol.* 153:517-528 (1994); Reference AX3 of record).

C. Whether claims 32, 112, 119, 125, 143, 148, 153 and 156 are properly rejected under 35 U.S.C. § 103(a) as being obvious over Butcher *et al.* (WO 94/13312; Reference AD of record) in view of Vonderheide *et al.* (U.S. Patent No. 5,599,676, Reference AB of record) and Erle *et al.* (*J. Immunol.* 153:517-528 (1994); Reference AX3 of record), and further in view of Capon *et al.* (U.S. Patent No. 5,565,335; Reference AF of record).

III. ARGUMENT

Appellant maintains that the rejections should be reversed for the reasons stated in the Amended Appeal Brief and the Reply Brief that was filed on January 16, 2007. This Reply Brief addresses the §103 rejections (Issues B and C in the Reply Brief filed January 16, 2007) in light of the recent KSR v. Teleflex, 127 S. Ct. 1727, 82 USPQ2d 1385 (2007) and Ex parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Inter. 2007) decisions.

Issue B. The Rejection of Claims 24-26, 28-31, 105-108, 111, 113, 115, 116, 118, 120, 121, 124, 126-142, 144-147, 149, 150, 152, 154, 155 and 157-160 under 35 U.S.C. 103(a) over Butcher *et al.* in view of Vonderheide *et al.* and Erle *et al.* Should be Reversed Because it is Contrary to Mandatory Legal Authority.

The rejection is inconsistent with In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995) and Ex parte Goldgaber, 41 USPQ2d 1172 (Bd. Pat. App. & Inter. 1995), because the disclosure in the cited references does not establish a *prima facie* case and would not have led inevitably to the claimed nucleic acids. The obviousness standards articulated in KSR and Kubin are not inconsistent with Deuel and Goldgaber, and do not bolster the appealed rejections.

KSR v. Teleflex

In KSR, the Court clarified the appropriate analysis for determining obviousness under 35 U.S.C. § 103. The Court restated that the Graham framework controls the analysis. Namely, explicit findings as to (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) secondary considerations, such as commercial success, long felt but unsolved needs, failure of others, etc., should be made. The legal question of obviousness is then assessed against this factual background.

The Court further clarified that under appropriate circumstances, an invention may properly be held obvious under a so-called "obvious to try" rationale.

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of

> ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 127 S. Ct. at 1742, 82 USPQ2d at 1397.

Nevertheless, the Court continues to require that a *prima facie* obviousness case requires an apparent reason why a person of ordinary skill in the art would combine the references, and the analysis must be made explicit. KSR, 127 S. Ct. at 1741, 82 USPQ2d at 1396.

In reaching this conclusion, the court discussed situations where an "obvious to try" rationale could be used to properly find a claimed invention obvious. One of the situations discussed by the Court can be described as "obvious to combine." This situation arises when known elements are combined to make a novel combination. The Court explained that under such circumstances, a "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield *predictable* results." KSR 127 S. Ct. at 1739, 82 USPQ2d at 1395. *Emphasis added.*

Another situation discussed by the Court can be described as "obvious to improve or vary." This situation arises when a technique that is known to be useful for improving or varying a device is used to improve or vary a similar device. The court explained that under these circumstances, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. ... [A] court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at 1740, 82 USPQ2d at 1396.

KSR is not inconsistent with the case law relied upon in the Amended Appeal Brief and the Reply Brief filed January 16, 2007. The Court did not overturn the "TSM" (teaching-suggestion-motivation) test for determining whether an invention is obvious under 35 U.S.C. § 103; rather, the Court disapproved of the narrow manner in which it was applied by the Federal Circuit in KSR. KSR, 127 S. Ct. at 1741, 82 USPQ2d at 1397. The Court indicated that the TSM test provided "helpful insight" and further said that there is no inconsistency between the TSM test and the Graham analysis. Id., 82 USPQ2d at 1396. The Court did not discount that the

test might serve as a useful analytical device in the context of a proper obviousness analysis. Id., 82 USPQ2d at 1396.

Ex parte Kubin

Kubin is the first precedential decision of the Board on the issue of obviousness decided after the Supreme Court's KSR opinion. The Board held that claims drawn to a genus of isolated nucleic acid encoding the protein NAIL (also referred to as p38) were not patentable because it would have been obvious to isolate at least one nucleic acid encompassed by the claims with a reasonable expectation of success. Kubin, 83 USPQ2d at 1414.

The scope and content of the prior art in Kubin included disclosures of the p38 polypeptide encoded by the claimed nucleic acids, a detailed method of isolating DNA encoding p38, and a "specific probe" (monoclonal antibody C1.7) for use in isolating the DNA. Id. at 1412.

The differences between the prior art and the claims at issue were very small, because the p38 disclosed in the prior art was the same protein as the NAIL protein of the claims at issue. Id. at 1413.

The level of ordinary skill in the art was high and methods of making the claimed nucleic acid sequences were known, as were methods of isolating clones. Id.

The Board framed the §103(a) issue as "[w]ould Appellants' claimed nucleotide sequence have been obvious to one of ordinary skill in the art, based on Valiante's disclosure of p38 and his express teachings how to isolate its cDNA by conventional techniques?" Id. The Board cited KSR, stating that "obvious to try" may be an appropriate test in more situations than previously contemplated. Kubin, 83 USPQ2d at 1414.

Against the factual background, the Board concluded that the generic claims were obvious because the problem of isolating NAIL cDNA was apparent to one of ordinary skill in the art, and there were a limited number of methodologies to do so. The Board reasoned that the skilled artisan would have had motivation to try these methodologies with the reasonable expectation that at least one would be successful. Id. at 1414. Importantly, Kubin did not argue the appealed claims separately, and consequently a single obvious species of nucleic acid was

sufficient to render the generic claims obvious. The Board did not consider whether particular species of nucleic acids might be obvious.

Also important, the Board noted that Deuel did not prevent this conclusion due to factual differences and increased level of skill in the art. Id. at 1413.

The facts in Deuel show that the case is distinguishable from Kubin and is consistent with KSR. In Deuel, the prior art disclosed a 19 amino acid N-terminal sequence of a brain specific "heparin-binding brain mitogen" that happened to match the N-terminal sequence of human and bovine placental HBGF disclosed in Deuel's application[1], and a reference describing methods for isolating DNA by screening a library using a gene probe. Deuel, 51 F.3d at 1556, 34 USPQ2d at 1213. The claims at issue were drawn to isolated DNAs that encode a placental HBGF defined by amino acid sequence, or to isolated cDNAs defined by nucleotide sequences that encode placental HBGFs. Id. at 1555, 34 USPQ2d at 1212. Importantly, the prior art in Deuel did not disclose a nucleic acid probe that would specifically hybridize to a cDNA encoding placental HBGF. In view of these facts, the Deuel court stated that a general motivation to search for a gene "does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search. More is needed and it is not found here." Id. at 1558, 34 USPQ2d at 1215.

These facts distinguish Kubin, because in Kubin all that needed to be done to arrive at the claimed nucleic acid was to follow the detailed teachings of the prior art using the disclosed antibody probe.[2] In Deuel, the prior art contained only a generalized motivation to search for some gene that exists, and did not disclose any relevant cDNA or isolated polypeptides or any specific "probes" that might be used to isolate the claimed cDNA. Under these facts, the Deuel court's reversal of the obviousness rejections comports with the Supreme Court's analysis in KSR, because the content of the prior art in Deuel was not sufficient to provide predictable results in the search for the claimed DNAs.

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[1] The sequence of the heparin-binding brain mitogen was not disclosed in the prior art and there was no evidence that the brain specific heparing-binding brain mitogen was the same as or related to placental HBGF.

[2] The facts of Kubin are similar to those in Goldgaber where the Board found the claimed nucleic acids obvious in view of the prior art disclosure of the amino acid sequence (of APP) encoded by the claimed nucleic acids and two sets of oligonucleotide probes suitable for use in isolated the gene that encodes APP. See, Amended Appeal Brief at 39-41.

1. The rejection should be reversed because the combined teachings of the cited references do not establish a *prima facie* case under 35 U.S.C. § 103 under an "obvious to try" rationale.

According to the rejection of record, it would have been obvious to make the claimed invention because Butcher *et al.* teach murine MAdCAM/Ig fusion proteins and Vonderheide *et al.* and Erle *et al.* provide the means to produce human or primate MAdCAM protein.

The claimed invention is not obvious over the cited references because none of the references either individually or in combination suggests the claimed fusion proteins. Additionally, a Graham analysis reveals that an "obvious to try" rationale is not appropriate because the facts of this case do not demonstrate there were a finite number of predictable solutions, or that the results that were achieved were expected.

Scope and Content of the Prior Art

Butcher *et al.* teaches fusion proteins comprising murine MAdCAM and an Ig constant region. Vonderheide *et al.* discloses and claims a general method for isolating a cDNA that encodes an α4 integrin receptor. There is no mention of human MAdCAM or disclosure of even one α4 integrin receptor in Vonderheide *et al.* Erle *et al.* expressly teach that the human homologue of MAdCAM-1 had not been identified, and consequently they used transfected cells that expressed murine MAdCAM-1 in their experiments. Erle *et al.* does not teach that human MAdCAM binds to α4β7.

The prior art does not teach primate MAdCAM or any suitable probes that might be used to search for primate MAdCAM. Moreover, the prior art is devoid of any nucleotide sequence data, any amino acid sequence data or any other teachings that would have suggested the particular claimed fusion proteins to the person of ordinary skill in the art.

Differences Between the Prior Art and the Claims at Issue

The prior art relates to murine MAdCAM. The claims at issue relate to primate or human MAdCAM, which have a very low degree of sequence similarity to murine MAdCAM.[3]

Level of Ordinary Skill in the Art

The level of ordinary skill in the art was high.

Lack of Predictability and Success

As discussed in the Amended Appeal Brief, attempts to isolate a cDNA encoding primate MAdCAM using gene probes based on the sequence of mouse MAdCAM under low stringency conditions were not successful, even though this approach is conventional in the art. Later it was determined that murine MAdCAM and primate MAdCAM have such a low degree of sequence similarity, and that this explained why conventional hybridization approaches were not successful. See, Amended Appeal Brief at 34, and Shyjan *et al.* Reference AX4 at 2853. The lack of success in cloning primate MAdCAM using low stringency hybridization is evidence that there was not a predictable solution for isolating primate MAdCAM available to persons of ordinary skill in the art.

Thus, recent case law demonstrates that Deuel is still applicable to the facts of this case and that the rejection should be reversed for the reasons stated previously in the Amended Appeal Brief and the first Reply Brief. Moreover, the rejection should be reversed because the Graham framework analysis presented above shows that the facts of this case do not support a rejection based on the "obvious to try" rationale presented in KSR and Kubin because there were not a finite number of predictable solutions to the problem solved by the claimed invention, and therefore the results achieved could not have been expected by one of ordinary skill in the art. As a result, the claimed invention is not obvious.

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[3] The amino acid sequence similarities were determined to be 78.5% between mouse and rat MAdCAM-1, 44.3% between mouse and macaque, and 39% between murine and MAdCAM-1 encoded by human Clone 4. Specification at 58, lines 9-12.

a. A *prima facie* case against claims 24-26, 28-31, 105-108, 111, 113, 115, 116, 118, 120, 121, and 124 has not been established.

A *prima facie* case has not been established against claims 24-26, 28-31, 105-108, 111, 113, 115, 116, 118, 120, 121, and 124 because the combined teachings of the cited references fail to suggest the amino acid sequence of a naturally occurring primate or human MAdCAM that binds α4β7 integrin and has at least 75% amino acid sequence similarity to SEQ ID NO:2, 4 or 6. Furthermore, these claims cannot be properly rejected under an "obvious to try" rationale for the reasons discussed herein. At best, the cited references provide a research plan that might have been used to search for primate or human MAdCAM with uncertain and unpredictable results.

b. A *prima facie* case against claims 136-142, 144-147, 149, 150, 152, 154, 155 and 157-160 has not been established

A *prima facie* case has not been established against claims 136-142, 144-147, 149, 150, 152, 154, 155 and 157-160, which recite at least 90% amino acid sequence similarity to SEQ ID NO:2, 4 or 6. These claims are drawn to a smaller subgenus of fusion proteins than claims that recite at least 75% amino acid sequence similarity, and therefore a more precise motivation or suggestion must be found in the prior art to establish a *prima facie* case. However, there is nothing in the combined teachings of the cited references that suggest an amino acid sequence that meets the limitation of the claims. Furthermore, these claims cannot be properly rejected under an "obvious to try" rationale for the reasons discussed herein. At best, the cited references provide a research plan that might have been used to search for primate or human MAdCAM with uncertain and unpredictable results.

c. A *prima facie* case against claims 126-135 has not been established.

Claims 126-135 recite that the fusion protein comprises a primate MAdCAM moiety that has a particular amino acid sequence (SEQ ID NO:2 or SEQ ID NO:4) or comprises an α4β7 integrin binding portion of a polypeptide that has a particular amino acid sequence (SEQ ID NO:2 or SEQ ID NO:4) and comprises the N-terminal immunoglobulin-like domain.

The cited combination of references contains no teaching that reasonably suggests the amino acid sequence of SEQ ID NO:2, the amino acid of SEQ ID NO:4, the amino acid sequence of an α4β7 integrin binding portion of SEQ ID NO:2 which comprises the N-terminal immunoglobulin-like domain, or the amino acid sequence of an α4β7 integrin binding portion of SEQ ID NO:4 which comprises the N-terminal immunoglobulin-like domain, to a person of ordinary skill in the art. Furthermore, these claims cannot be properly rejected under an "obvious to try" rationale for the reasons discussed herein. At best, the cited references provide a research plan that might have been used to search for primate or human MAdCAM with uncertain and unpredictable results.

Issue C. The Rejection of Claims 32, 112, 119, 125, 143, 148, 153 and 156 under 35 U.S.C. § 103(a) over Butcher *et al.*, in view of Vonderheide *et al.*, Erle *et al.* and further in view of Capon *et al.* Should be Reversed Because it is Contrary to Mandatory Legal Authority.

The Examiner's Answer did not present any new remarks in support of the rejections of record. Appellant maintains that the rejection should be reversed for the reasons above, the reasons stated in the Amended Appeal Brief, and the reasons stated in the first Reply Brief.

1. A *prima facie* case against claims 32, 112, 119 and 125 has not been established.

The claims are not obvious and the rejection should be reversed for the reasons discussed herein with respect to the "Issue B" rejection of claims 24-26, 28-31, 105-108, 111, 113, 115, 116, 118, 120, 121 and 124. Capon *et al.* adds nothing to the rejection because Capon *et al.* contains no teachings that relate to primate or human MAdCAM or that suggest the claimed fusion proteins. Accordingly, the combined teachings of the references fail to suggest the claimed fusion proteins. Moreover, the addition of Capon *et al.* does not substantially change the factual background against which the legal question of obviousness is determined. Therefore, these claims are not properly rejected under the "obvious to try" rationale of KSR or Kubin.

2. A *prima facie* case against claims 143, 148, 153 and 156 has not been established.

The claims are not obvious and the rejection should be reversed for the reasons discussed herein with respect to the "Issue B" rejection of claims 136-142, 144-147, 149, 150, 152, 154, 155 and 157-160. Capon *et al.* adds nothing to the rejection because Capon *et al.* contains no teachings that relate to primate or human MAdCAM or that suggest the claimed fusion proteins. Moreover, the addition of Capon *et al.* does not substantially change the factual background against which the legal question of obviousness is determined. Therefore, these claims are not properly rejected under the "obvious to try" rationale of KSR or Kubin.

CONCLUSION

In view of the foregoing, the arguments presented in the Amended Appeal Brief filed on August 16, 2006 and the Reply Brief filed on April 20, 2007, reversal of the rejections is requested.

Respectfully submitted,

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